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## Atoh1 Directs Regeneration and Functional Recovery of the Mature Mouse Vestibular System.

**Journal:** Cell Rep

**Publication Year:** 2019

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**PubMed link:** 31291569

**Funding Grants:** Enhancing hair cell regeneration in mouse and human inner ear , Modulation of the Wnt pathway to restore inner ear function

### Public Summary:

Hair cells are mechanoreceptors needed for vestibular function, such as to detect head rotation and position. Whether hair cell regeneration restores vestibular function in the mature mouse is not known. Here, by manipulating the transcription factor Atoh1, we enhanced hair cell regeneration leading to improved vestibular function.

### Scientific Abstract:

Utricular hair cells (HCs) are mechanoreceptors required for vestibular function. After damage, regeneration of mammalian utricular HCs is limited and regenerated HCs appear immature. Thus, loss of vestibular function is presumed irreversible. Here, we found partial HC replacement and functional recovery in the mature mouse utricle, both enhanced by overexpressing the transcription factor Atoh1. Following damage, long-term fate mapping revealed that support cells non-mitotically and modestly regenerated HCs displaying no or immature bundles. By contrast, Atoh1 overexpression stimulated proliferation and widespread regeneration of HCs exhibiting elongated bundles, patent mechanotransduction channels, and synaptic connections. Finally, although damage without Atoh1 overexpression failed to initiate or sustain a spontaneous functional recovery, Atoh1 overexpression significantly enhanced both the degree and percentage of animals exhibiting sustained functional recovery. Therefore, the mature, damaged utricle has an Atoh1-responsive regenerative program leading to functional recovery, underscoring the potential of a reprogramming approach to sensory regeneration.

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